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TO:	Mr. Ed Gross		**Company:**	U.S. EPA
	Attn: TSCA Section 8(e)			
	Fax #:	202-564-8955	**City/State:**	Washington, DC
	Tel. #:	202-564-8961		
FROM:	Anne Walsh	5540	**Our Ref. #:**	03398-044002

NUMBER OF PAGES (including transmittal sheet): 5

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Notes/Comments:

Mr. Gross:
Pursuant to our conversation today, I am faxing you a TSCA Section 8(e) submission of information. I understand you will consider it received as of the above date.

Thank you in advance,
Anne Walsh

MR 265205

FORMALDEHYDE EPIDEMIOLOGY, TOXICOLOGY, AND ENVIRONMENTAL GROUP, INC.

1730 PENNSYLVANIA AVENUE NW
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VIA FACSIMILE (202/564-8955)

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March 14, 2003

Document Processing Center
EPA East (Mail Code 7407M)
Attn: TSCA Section 8(e)
U.S. Environmental Protection Agency
1201 Constitution Avenue, N.W.
Washington, DC 20460-0001

Re: Submission of Information under TSCA Section 8(e)

Dear Sir or Madam:

I am writing on behalf of the Formaldehyde Epidemiology, Toxicology and Environmental Group, Inc. (FETEG), a trade association of formaldehyde and formaldehyde resin producers, and its member companies, including Borden Chemical, Inc., Celanese Ltd., Cytec Industries Inc., DuPont, Dynea USA, Inc., Georgia-Pacific Corporation, Solutia Inc., and UCB.

We have received a preliminary draft manuscript of a study of industrial workers exposed to formaldehyde from the National Cancer Institute (NCI) (Hauptmann, et al.). The manuscript may change during the peer review process, and the National Cancer Institute has asked that we neither quote nor distribute the draft paper. Within the bounds of that restriction, however, we wanted to inform EPA of the nature of the preliminary, draft findings.

The draft manuscript presents partial results from a cohort mortality study of industrial workers exposed to formaldehyde at ten facilities in the U.S. The study addresses the same cohort as the mortality study reported by Blair, et al., *J. Natl. Cancer Inst.* 76:1071 (1986). The study covers workers who began employment at a participating plant between 1938 and 1966. NCI has now followed causes of death in the cohort through 1994. However, less than 4% of the person-years of exposure in the study occurred after 1980, and thus the study does not address current workplace conditions.

The draft addresses only the findings of the study related to lymphohematopoietic cancers. Dr. Blair has informed us that a finding of nasopharyngeal cancer, consistent with previous findings, and a lack of lung cancer in the cohort will be addressed in a separate paper forthcoming shortly.

With regard to the lymphohematopoietic cancers, the authors report observing *fewer* deaths from these cancers than expected in both exposed and unexposed workers compared to rates in the U.S. population (SMR 0.80 for exposed workers, 0.62 for unexposed workers, both a statistically significant deficit). Leukemia in particular shows a statistically significant deficit in unexposed workers compared to the general population (SMR 0.38, statistically significant). All causes of death, all cancers, all solid malignant neoplasms, circulatory diseases, and respiratory diseases also occur at lower rates than expected in both exposed and unexposed workers. These findings of less disease than the U.S. population in the workers appear to go beyond the "healthy worker effect" often observed in occupational populations.

The draft report does not present any comparisons to expected general population rates stratified by exposure group. However, the authors do present comparisons to internal reference groups stratified by various measures of exposure. The draft report indicates that relative risk for leukemia is increased approximately three-fold when workers exposed to peak exposure concentrations ≥ 4 ppm or average exposure concentrations ≥ 1 ppm are compared to unexposed workers, with a trend noted for peak exposure. The report provides similar results using the low-exposure groups as internal reference groups. However, the authors report no relationship between leukemia and either duration of exposure or cumulative exposure using internal comparison groups. Some evidence for an excess of Hodgkin's disease is noted, based on comparison of high peak or average exposure compared to low exposure categories, and a trend for exposure.

The draft report indicates these data are suggestive of an association between formaldehyde and leukemia and possibly other lymphohematopoietic cancers, but the authors suggest caution in drawing any definitive conclusions from the study. Excesses of leukemia or other lymphohematopoietic cancers were not seen in the earlier study of the cohort, and have not previously been observed in industrial workers.

Significantly, the NCI authors report that their draft findings are inconsistent with a study of British industrial workers exposed to formaldehyde by Coggon, et al. The Coggon paper, which finds no excess of leukemia in industrial workers, is to be published in the same issue of the *Journal of the National Cancer Institute* as the forthcoming NCI paper.

As noted above, the NCI authors suggest caution in drawing any definitive conclusion from the study, and they have reminded us that the draft is likely to change over the course of peer review prior to publication. Moreover, the authors have proposed further research to explore the draft findings on leukemia.

With NCI's permission, FETEG has asked a distinguished panel of peer reviewers to assist us in providing comments to NCI on the draft manuscript. We are still in the process of collating the peer review input and will be providing detailed peer review comments to the NCI researchers next week. In general, however, the peer reviewers have questioned whether the suggested association with leukemia is valid or causally related to formaldehyde in light of:

- The biologic implausibility of an association between lymphohematopoietic cancer (blood and bone marrow system cancers, including leukemia) and formaldehyde, given
  - extensive animal study data that do not show leukemia in animals exposed to formaldehyde;
  - the absence of formaldehyde-DNA protein cross-link formation in the bone marrow of rats exposed to radiolabeled formaldehyde;
  - the absence of an increase in the formaldehyde concentration in blood in humans, monkeys or rats exposed to airborne formaldehyde;
  - the evidence of normal metabolic pathways handling formaldehyde at inhaled concentrations less than 2 ppm; and
  - the lack of evidence of cytogenetic damage in rat lymphocytes and bone marrow cells after exposure to very high concentrations of formaldehyde.

  Extensive toxicokinetic and metabolic studies in laboratory animals and humans indicate that the vast majority of inhaled formaldehyde is deposited within the upper respiratory tract, and tumors at distant sites are not expected.
- The finding of *fewer* than expected deaths from all cancers, including leukemia, in both exposed and unexposed workers at the plants in the study.
- The finding of *notably fewer* than expected deaths from leukemia in unexposed workers at these plants, suggesting that the exposed and unexposed groups may differ in some way other than formaldehyde exposure.
- The draft report's lack of comparison of the exposure-stratified groups to national or regional cancer rates as opposed to internal reference groups.
- The lack of an association between leukemia and either cumulative dose or duration of exposure to formaldehyde.
  - The draft report cites the possibility of leukemia being associated with formaldehyde based on peak exposure, comparing this to leukemia from short-term benzene or radiation exposure. However, leukemia is also known to be associated with *chronic* benzene exposure, and thus would be related to cumulative exposure or duration of exposure. If leukemia is associated with short-term exposure to formaldehyde, it is puzzling why an increase in leukemia was not observed in the original study of this cohort, which included many years of follow-up.
- The lack of adequate discussion or analysis of potential confounding by benzene or other exposures known to be present in some of the workplaces.
- The absence of analysis showing whether the results are focused at any single plant, particularly given the unusually wide variety of types of plants in the study.

- Unexplained changes in exposure categories and classifications even though the exposure assessment has not been updated since the 1986 publication.
- The lack of consistency with findings of other studies of industrial workers.

We hope that many of these questions will be answered during the peer review process. We nonetheless are providing this notice under TSCA Section 8(e) because the draft NCI suggestion of increased leukemia in an industrial population exposed to formaldehyde, if valid, would be a new finding, and our members take any issue of workplace health and safety seriously.

Should you have any questions for us, you may reach us through our counsel, Katherine Rhyne, at 202-626-3743, or our spokesperson, Mike Heimowitz, at 202-955-6200.

Sincerely,

James P. Mieure by KR

James P. Mieure, Ph.D.
President, FETEG